Corneal Crosslinking Without Epithelial Removal

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Financial Disclosures

- Abbott Medical Optics
- Alcon Laboratories
- Avedro
- Calhoun Vision
- Cambium Medical Technologies
- CXL Ophthalmics
- EyeYon

- Hydrolenz
- Intelon
- Ocumetrics
- Ophtec
- Primisight
- TearLab
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- Ophtec
- Primisight
- TearLab
Methods
Methods

- Prospective, observational study
- Novel riboflavin formulation and loading technique\(^1\)
- Physician verification of riboflavin concentration, location, and homogenity at 20 min. with additional loading as needed (5-10 min)
- 12mm diameter light
- No riboflavin during UVA exposure
- Pulsed UVA
- 4 mW/cm\(^2\)

\(^1\) Patented riboflavin solution with optimized osmolarity, pH, concentration, nontoxic additive and delivery system developed by CXL Ophthalmics
Ex Vivo Rabbit Corneas

Commercially Available Formulation
ParaCel 4 min. and VibeX 6 min. per label

CXLUSA Formulation
CXLUSA formulation and loading sponges 10 min.

Independent study performed by Absorption Systems, Inc., San Diego, CA, reported October 13, 2015
Ex Vivo Rabbit Corneas

Commercially Available Formulation

ParaCel 4 min. and VibeX 6 min. per label

CXLUSA Formulation

CXLUSA formulation and loading sponges 10 min.

Independent study performed by Absorption Systems, Inc., San Diego, CA, reported October 13, 2015
Corneal Riboflavin Concentration
($\mu$g/g at 20-25 min.)

- Commercially Available Formulation (ParCel + VibeX)
- CXLUSA Formulation

Liquid chromatography/tandem mass spectrometry
Independent study performed by Absorption Systems, Inc., San Diego, CA, reported October 13, 2015
Inclusion Criteria

- Keratoconus, PMD, ectasia, FFKC
- 8-yo min.
- $CT_{\text{min}}$: 300µ
Enrollment

- October 17, 2013-April 26, 2016
- 608 eyes with ectatic disease (10-65 yo)
  - Keratoconus: 512
  - Ectasia: 80
  - PMD: 16
- CTmin: 302µ
- Database freeze 11/17/16
Interim Analysis

- Keratoconus or ectasia (excluding PMD)
  - 592 eyes total
  - 295 eyes with 12-month exams
  - 97 eyes with 24-month exams
  - 79 eyes (consistent cohort) with
    - 3, 6, 12, and 24-month exams
    - UCVA, MR, BSCVA, and Pentacam
Subject ATL-003

Keratoconus

Preop 3 6 12 Months After Surgery

UCVA (20/-)  BSCVA (20/-)

20/100  20/60  20/30  20/50  20/50

20/100  20/60  20/50  20/25  20/20

15 yof
### 12-Month Followup

**n=295**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preop</th>
<th>12 mos</th>
<th>Change</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCVA (20/-)</td>
<td>148.3</td>
<td>110.5</td>
<td>~1 line</td>
<td></td>
</tr>
<tr>
<td>CDVA (20/-)</td>
<td>34.8</td>
<td>28.3</td>
<td>~1 line</td>
<td></td>
</tr>
<tr>
<td>Kmax</td>
<td>56.14</td>
<td>55.71</td>
<td>-0.44</td>
<td></td>
</tr>
<tr>
<td>Total HOA</td>
<td>1.262</td>
<td>0.886</td>
<td>-0.408</td>
<td>-29.8</td>
</tr>
<tr>
<td>Total Coma</td>
<td>1.041</td>
<td>0.718</td>
<td>-0.342</td>
<td>-31.1</td>
</tr>
</tbody>
</table>
Will We See Progression After One Year?

Caporosi et al. JCRS 2013;391:1157

Soeters et al., AJO 2015;159:821
Visual Acuities
Consistent Cohort at 24 Months

- UCVA ~1 1/2 lines
- BSCVA ~1 1/2 lines

No loss from 1-2 yr

N=79
Topography
Consistent Cohort at 24 Months

Months After Surgery

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kmax (D)</strong></td>
<td>56.68</td>
<td>56.49</td>
<td>56.42</td>
<td>56.21</td>
<td>56.14</td>
</tr>
<tr>
<td><strong>Kave (D)</strong></td>
<td>47.82</td>
<td>47.83</td>
<td>47.82</td>
<td>47.81</td>
<td>47.84</td>
</tr>
<tr>
<td><strong>Zonal mean K (D)</strong></td>
<td>46.58</td>
<td>46.43</td>
<td>46.51</td>
<td>46.54</td>
<td>46.49</td>
</tr>
</tbody>
</table>

N=79

Kmax ↓ 0.54 D
No increase from 1-2 years
High-Order Aberrations
Consistent Cohort at 24 Months

<table>
<thead>
<tr>
<th>Months After Surgery</th>
<th>Total</th>
<th>Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>1.34</td>
<td>1.11</td>
</tr>
<tr>
<td>3</td>
<td>1.28</td>
<td>1.08</td>
</tr>
<tr>
<td>6</td>
<td>1.30</td>
<td>1.10</td>
</tr>
<tr>
<td>12</td>
<td>0.97</td>
<td>0.81</td>
</tr>
<tr>
<td>24</td>
<td>0.79</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Mean RMS

- 41% Reduction in total HOA
- 42% Reduction in coma
- No increase from 1-2 years

N=79
Subject ATL-003 OD
14 yof with Keratoconus

Preop 3 6 12 24
Months After Surgery

UCVA (20/-)
BSCVA (20/-)

20/400 20/100 20/60 20/30 20/50 20/25 20/50 20/20 20/20
Subject ATL-003 OD
14 yof with Keratoconus

Preop 3 6 12 24 Months After Surgery

UCVA (20/-)
BSCVA (20/-)

20/400
20/100
20/60
20/30
20/50
20/25
20/50
20/20
20/20
20/20
20/50
Subject ATL-003 OD
14 yof with Keratoconus

Kmax \( \downarrow \) 2.2 D
Continued decrease from 1-2 years

<table>
<thead>
<tr>
<th>Months After Surgery</th>
<th>Preop</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kmax (D)</td>
<td>51.60</td>
<td>50.40</td>
<td>50.60</td>
<td>50.60</td>
<td>49.40</td>
</tr>
<tr>
<td>Kave (D)</td>
<td>45.80</td>
<td>45.60</td>
<td>45.50</td>
<td>46.50</td>
<td>45.30</td>
</tr>
<tr>
<td>Zonal mean K (D)</td>
<td>45.80</td>
<td>45.60</td>
<td>45.70</td>
<td>45.50</td>
<td>45.10</td>
</tr>
</tbody>
</table>
Case Reports
Subject ATL-124

10 yo hispanic female with KC

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>UCVA</th>
<th>BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op</td>
<td>20/200</td>
<td>20/40</td>
</tr>
<tr>
<td>3 Months</td>
<td>20/40</td>
<td>20/40</td>
</tr>
<tr>
<td>6 Months</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>12 Months</td>
<td>20/25</td>
<td>20/25</td>
</tr>
</tbody>
</table>

Right Eye

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>UCVA</th>
<th>BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op</td>
<td>20/200</td>
<td>20/40</td>
</tr>
<tr>
<td>3 Months</td>
<td>20/40</td>
<td>20/40</td>
</tr>
<tr>
<td>6 Months</td>
<td>20/25</td>
<td>20/25</td>
</tr>
<tr>
<td>12 Months</td>
<td>20/25</td>
<td>20/25</td>
</tr>
</tbody>
</table>

Left Eye

12 months | preop | difference

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>UCVA</th>
<th>BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op</td>
<td>20/80</td>
<td>20/30</td>
</tr>
<tr>
<td>3 Months</td>
<td>20/60</td>
<td>20/50</td>
</tr>
<tr>
<td>6 Months</td>
<td>20/40</td>
<td>20/25</td>
</tr>
<tr>
<td>12 Months</td>
<td>20/30</td>
<td>20/25</td>
</tr>
</tbody>
</table>
Subject ATL-078

OD  Not treated

OS  CXL 5/8/14

2 ½ years
Re-Treatments

1 eye during study
1 eye after study
Subject ATL-054 OD
16 yom with Keratoconus

12 months
Subject ATL-054 OD
16 yom with Keratoconus

Months After Surgery

Preop 3 6 12 3 6 12

UCVA (20/-)

CDVA (20/-)

Retreatment
Subject ATL-054 OD
16 yom with Keratoconus

Months After Surgery

Preop  3  6  12  3  6  12

UCVA (20/-)  CDVA (20/-)

Retreatment
Subject ATL-054 OD

16 yom with Keratoconus

12 months after re-treatment
Subject ATL-028 OS
58 yof with Ectasia

24 months
Subject ATL-028 OS
58 yof with Ectasia

UCVA (20/-)
CDVA (20/-)

Months After Surgery

Preop 3 6 12 24
20/400 20/400
20/100 20/200 20/200
20/40 20/30
Retreatment

20/40 20/30 20/40 20/30 20/40
Subject ATL-028 OS
58 yof with Ectasia

<table>
<thead>
<tr>
<th>Months After Surgery</th>
<th>UCVA (20/-)</th>
<th>CDVA (20/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>20/400</td>
<td>20/400</td>
</tr>
<tr>
<td>3</td>
<td>20/30</td>
<td>20/30</td>
</tr>
<tr>
<td>6</td>
<td>20/100</td>
<td>20/40</td>
</tr>
<tr>
<td>12</td>
<td>20/200</td>
<td>20/30</td>
</tr>
<tr>
<td>24</td>
<td>20/200</td>
<td>20/40</td>
</tr>
<tr>
<td>3</td>
<td>20/40</td>
<td>20/30</td>
</tr>
<tr>
<td>6</td>
<td>20/70</td>
<td>20/40</td>
</tr>
<tr>
<td>Retreatment</td>
<td>20/40</td>
<td>20/25</td>
</tr>
</tbody>
</table>

Note: UCVA (Uncorrected Visual Acuity) and CDVA (Corrected Distance Visual Acuity).
Subject ATL-028 OS
58 yof with Ectasia

6 months after re-treatment
What About Eyes With An Increase In Kmax?
CDVA When \( \uparrow \) Kmax > 1D at 12 mos

21/297 eyes at 12 months with \( \uparrow \) Kmax > 1D
CDVA When $\uparrow K_{\text{max}} > 1 \text{D at 12 mos}$

Average gain of 1.1 lines

Number of Eyes

- 4 lines worse
- 3 lines worse
- 2 lines worse
- 2 Lines Worse
- 1 Line Worse
- Equal to PreTx CDVA
- 1 Line Better
- 2 Lines Better
- 3 lines better
- 4 lines better

$n=21$
CDVA When $K_{max} > 1D$ at 12 mos

No eyes with $K_{max} > 1D$ and loss of >1 line CDVA

$n=21$
CDVA When \( \uparrow K_{max} > 1D \) at 24 mos

11/97 eyes at 24 months with \( \uparrow K_{max} > 1D \)
CDVA When \( \uparrow K_{\text{max}} > 1 \text{D} \) at 24 mos

Average gain of 1.1 lines

Number of Eyes

- 4 lines worse: 0
- 3 lines worse: 1
- 2 lines worse: 2
- 2 Lines Worse: 2
- 1 Line Worse: 1
- Equal to PreTx CDVA: 3
- 1 Line Better: 1
- 2 Lines Better: 2
- 3 lines better: 3
- 4 lines better: 4

\( n=11 \)
No eyes with $\uparrow \text{Kmax} > 1\text{D}$ and loss of $>1$ line CDVA

CDVA When $\uparrow \text{Kmax} > 1\text{D}$ at 24 mos

Number of Eyes

- 4 lines worse
- 3 lines worse
- 2 lines worse
- 2 lines Worse
- 1 Line Worse
- Equal to PreTx CDVA
- 1 Line Better
- 2 Lines Better
- 3 lines better
- 4 lines better

$n=11$
Adverse Events
Adverse Events
ATL-051 OD

• Hydrops
  » 1 eye with ectasia at 23 months
  » Underwent PK

<table>
<thead>
<tr>
<th></th>
<th>UCVA</th>
<th>CDVA</th>
<th>Kmax¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>20/400</td>
<td>20/400</td>
<td>72.0</td>
</tr>
<tr>
<td>24 months</td>
<td>20/400</td>
<td>20/200</td>
<td>79.4</td>
</tr>
</tbody>
</table>

¹Data gaps on all Pentacam exams
Adverse Events
ATL-185 OS

• Scleritis
  » 1 eye with KC at 3 weeks
  » Responded to oral steroids

<table>
<thead>
<tr>
<th></th>
<th>UCVA</th>
<th>CDVA</th>
<th>Kmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>20/50</td>
<td>20/25</td>
<td>58.5</td>
</tr>
<tr>
<td>24 months</td>
<td>20/30</td>
<td>20/20</td>
<td>59.1</td>
</tr>
</tbody>
</table>
Adverse Events
ATL-037 OD

- Disciform edema
  - 1 eye with KC at 15 mos
  - On Valtrex 500 mg qd for oral HSV
  - Responded to Valtrex 1 gm BID and topical steroids

<table>
<thead>
<tr>
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<th>UCVA</th>
<th>CDVA</th>
<th>Kmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>20/400</td>
<td>20/30</td>
<td>58.2</td>
</tr>
<tr>
<td>24 months</td>
<td>20/400</td>
<td>20/20</td>
<td>56.7</td>
</tr>
</tbody>
</table>
Conclusions

- Epi-on CXL using CXLO technologies halts progression of ectatic corneal disease without loss of effect between 1 and 2 years
- Improvement in CDVA is similar to that with epi-off CXL
- No complications of epithelial removal
- No eyes with > 1D increase in Kmax and loss of > 1 line CDVA
- No AE’s resulting in visual loss
- Kmax may not be best metric for evaluating CXL
Thank You
Differences In Technique

- BAC or Tris + EDTA
- No physician assessment of saturation
- Riboflavin during UVA exposure
- 9 mm diameter light
- Continuous UVA
- 3 mW/cm²

- Novel riboflavin formulation¹
- Physician SL verification and saturation as needed
- No riboflavin during UVA exposure
- 12 mm diameter light
- Pulsed UVA
- 4 mW/cm²

¹Patented riboflavin with optimized osmolarity, pH, concentration, non-toxic additive and delivery system developed by CXL Ophthalmics
Demarcation Lines

CXLUSA

Photo Courtesy of Dan Goodman, MD

0.1% Riboflavin + THAM + EDTA

Filipello, JCRS 2012;38:238
Slit Lamp Grading System

Grade 0/V

Grade I/V
Slit Lamp Grading System

Grade II/V

Grade III/V
Slit Lamp Grading System

Grade IV/V

Grade V/V
Slit Lamp Grade

Commercially Available Formulation (ParaCel, VibeX Xtra)

CXLUSA Formulation

3 Rabbits

4 Rabbits